



Clinical trial results:

A phase III, partially double-blind clinical trial to evaluate the immunogenicity and reactogenicity of GlaxoSmithKline (GSK) Biologicals' combined Infanrix hexa vaccine (new formulation) as compared with GSK Biologicals' combined Infanrix hexa vaccine (current formulation) administered in healthy infants at 3, 4 and 5 months of age. The immunogenicity, safety and reactogenicity of the DTPa-HBV-IPV vaccine will also be evaluated in a third group of subjects.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2012-002427-15 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 25 January 2007 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 11 May 2016 |
| First version publication date | 25 June 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 105910 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00320463 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | GlaxoSmithKline Biologicals |
| Sponsor organisation address | Rue de l'Institut 89, Rixensart, Belgium, B-1330 |
| Public contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 June 2007 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 January 2007 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 January 2007 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the immunogenicity of the Infanrix hexa vaccine (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing Infanrix hexa vaccine one month after a three-dose primary vaccination course

Protection of trial subjects:

All subjects were supervised after vaccination/product administration with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 28 April 2006 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Russian Federation: 417 |
| Worldwide total number of subjects | 417 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 417 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

The study was double-blind with respect to the 2 Infanrix Hexa Groups and single-blind with respect to the Infanrix Penta Group. Infanrix TM Hexa vaccine (preservative-containing) was used as a control in this study.

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Infanrix Hexa NEW Group |

Arm description:

Subjects who received the preservative-free formulation of the Infanrix hexa vaccine

| | |
|--|-----------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Infanrix TM Hexa |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Three doses of vaccine were administered intramuscularly into the anterolateral quadrant of the right thigh at 3, 4 and 5 months of age.

| | |
|------------------|-------------------------|
| Arm title | Infanrix Hexa REF Group |
|------------------|-------------------------|

Arm description:

Subjects who received the preservative-containing formulation of the Infanrix hexa vaccine

| | |
|--|-----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Infanrix TM Hexa |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Three doses of vaccine were administered intramuscularly into the anterolateral quadrant of the right thigh at 3, 4 and 5 months of age.

| | |
|------------------|----------------------|
| Arm title | Infanrix Penta Group |
|------------------|----------------------|

Arm description: -

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-------------------|
| Investigational medicinal product name | Infanrix™ penta |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Three doses of vaccine were administered intramuscularly into the anterolateral quadrant of the right thigh at 3, 4 and 5 months of age.

| Number of subjects in period 1 | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group |
|---------------------------------------|-------------------------|-------------------------|----------------------|
| Started | 167 | 167 | 83 |
| Completed | 163 | 165 | 82 |
| Not completed | 4 | 2 | 1 |
| Consent withdrawn by subject | 2 | 1 | 1 |
| Migrated/moved from study area | 1 | 1 | - |
| Unspecified | 1 | - | - |

Baseline characteristics

Reporting groups

| | |
|--|-------------------------|
| Reporting group title | Infanrix Hexa NEW Group |
| Reporting group description: | |
| Subjects who received the preservative-free formulation of the Infanrix hexa vaccine | |
| Reporting group title | Infanrix Hexa REF Group |
| Reporting group description: | |
| Subjects who received the preservative-containing formulation of the Infanrix hexa vaccine | |
| Reporting group title | Infanrix Penta Group |
| Reporting group description: - | |

| Reporting group values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group |
|---|-------------------------|-------------------------|----------------------|
| Number of subjects | 167 | 167 | 83 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: weeks | | | |
| arithmetic mean | 12.9 | 13 | 12.9 |
| standard deviation | ± 1.27 | ± 1.32 | ± 1.28 |
| Gender categorical Units: Subjects | | | |
| Female | 79 | 69 | 51 |
| Male | 88 | 98 | 32 |

| Reporting group values | Total | | |
|--|--------------------------------------|--|--|
| Number of subjects | 417 | | |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years | 0 0 0 0 0 0 0 0 | | |

| | | | |
|-------------------|---|--|--|
| 85 years and over | 0 | | |
|-------------------|---|--|--|

| | | | |
|---|-----|--|--|
| Age continuous Units: weeks arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 199 | | |
| Male | 218 | | |

End points

End points reporting groups

| | |
|--|-------------------------|
| Reporting group title | Infanrix Hexa NEW Group |
| Reporting group description: Subjects who received the preservative-free formulation of the Infanrix hexa vaccine | |
| Reporting group title | Infanrix Hexa REF Group |
| Reporting group description: Subjects who received the preservative-containing formulation of the Infanrix hexa vaccine | |
| Reporting group title | Infanrix Penta Group |
| Reporting group description: - | |

Primary: Number of seroprotected subjects against Hepatitis B (anti-HBs) antigen with cut off value of 10 mIU/mL

| | |
|--|---|
| End point title | Number of seroprotected subjects against Hepatitis B (anti-HBs) antigen with cut off value of 10 mIU/mL |
| End point description: | |
| End point type | Primary |
| End point timeframe: At one month after (POST) Dose 3 | |

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|-------------------------------|-------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 116 | 123 | 63 | |
| Units: Subjects | | | | |
| Anti-HBs, POST (N=116,123,63) | 115 | 121 | 61 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference in seroprotection rates for anti-HBs |
| Statistical analysis description: To demonstrate that the immunogenicity of the Infanrix hexa vaccine (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing Infanrix hexa vaccine one month after a three-dose primary vaccination course. | |
| Comparison groups | Infanrix Hexa NEW Group v Infanrix Hexa REF Group |
| Number of subjects included in analysis | 239 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Difference in seroprotection rate |
| Point estimate | -0.76 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -4.97 |
| upper limit | 3.24 |

Notes:

[1] - The upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix hexa(current formulation) minus Infanrix hexa(new formulation)] for the percentage of seroprotected subjects below 10%.

Primary: Number of seroprotected subjects against polyribosyl ribitol phosphate (anti-PRP) antigen with cut off value of 0.15 µg/mL

| | |
|-----------------|--|
| End point title | Number of seroprotected subjects against polyribosyl ribitol phosphate (anti-PRP) antigen with cut off value of 0.15 µg/mL |
|-----------------|--|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At one month after (POST) Dose 3

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|-------------------------------|-------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 104 | 106 | 54 | |
| Units: Subjects | | | | |
| Anti-PRP, POST (N=104,106,54) | 98 | 102 | 12 | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Difference in seroprotection rates for anti-PRP |
|----------------------------|---|

Statistical analysis description:

To demonstrate that the immunogenicity of the Infanrix hexa vaccine (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing Infanrix hexa vaccine one month after a three-dose primary vaccination course.

| | |
|---|---|
| Comparison groups | Infanrix Hexa NEW Group v Infanrix Hexa REF Group |
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Parameter estimate | Difference in seroprotection rate |
| Point estimate | 2 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.31 |
| upper limit | 8.74 |

Notes:

[2] - The upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix hexa(current formulation) minus Infanrix hexa(new formulation)] for the percentage of seroprotected subjects below 10%.

Primary: Number of seroprotected subjects against diphtheria (anti-D) and tetanus (anti-T) antigen with cut off value of 0.1 IU/mL.

| | |
|-----------------|--|
| End point title | Number of seroprotected subjects against diphtheria (anti-D) and tetanus (anti-T) antigen with cut off value of 0.1 IU/mL. |
|-----------------|--|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At one month after (POST) Dose 3

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|-----------------------------|-------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 104 | 106 | 54 | |
| Units: Subjects | | | | |
| Anti-D, POST (N=104,106,54) | 101 | 102 | 52 | |
| Anti-T, POST (N=104,106,54) | 103 | 106 | 54 | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Difference in seroprotection rates for Anti-D |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate that the immunogenicity of the **Infanrix hexa vaccine** (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing **Infanrix hexa vaccine** one month after a three-dose primary vaccination course.

| | |
|-------------------|--|
| Comparison groups | Infanrix Hexa NEW Group v Infanrix Hexa REF Group |
|-------------------|--|

| | |
|---|-----|
| Number of subjects included in analysis | 210 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|--------------------------------|
| Analysis type | non-inferiority ^[3] |
|---------------|--------------------------------|

| | |
|--------------------|-----------------------------------|
| Parameter estimate | Difference in seroprotection rate |
|--------------------|-----------------------------------|

| | |
|----------------|-------|
| Point estimate | -0.89 |
|----------------|-------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|------|
| lower limit | -6.8 |
|-------------|------|

| | |
|-------------|------|
| upper limit | 4.84 |
|-------------|------|

Notes:

[3] - The upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [**Infanrix hexa**(current formulation) minus **Infanrix hexa**(new formulation)] for the percentage of seroprotected subjects below 10%.

| | |
|-----------------------------------|---|
| Statistical analysis title | Difference in seroprotection rates for Anti-T |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate that the immunogenicity of the **Infanrix hexa vaccine** (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing **Infanrix hexa vaccine** one month after a three-dose primary vaccination course.

| | |
|---|---|
| Comparison groups | Infanrix Hexa NEW Group v Infanrix Hexa REF Group |
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in seroprotection rate |
| Point estimate | 0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.55 |
| upper limit | 5.25 |

Primary: Number of seroprotected subjects against Poliomyelitis (anti-Polio 1, anti Polio2, Anti-Polio 3) antigen with cut off value of 8.

| | |
|----------------------------------|---|
| End point title | Number of seroprotected subjects against Poliomyelitis (anti-Polio 1, anti Polio2, Anti-Polio 3) antigen with cut off value of 8. |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| At one month after (POST) Dose 3 | |

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|--------------------------------|-------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 74 | 37 | |
| Units: Subjects | | | | |
| Anti-Polio1, POST (N=60,66,31) | 60 | 66 | 31 | |
| Anti-Polio2, POST (N=64,74,36) | 64 | 74 | 36 | |
| Anti-Polio3, POST (N=71,72,37) | 71 | 72 | 37 | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Seroprotection rates difference for anti-Polio 1 |
| Statistical analysis description: | |
| To demonstrate that the immunogenicity of the Infanrix hexa vaccine (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing Infanrix hexa vaccine one month after a three-dose primary vaccination course. | |
| Comparison groups | Infanrix Hexa NEW Group v Infanrix Hexa REF Group |

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 145 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[4] |
| Parameter estimate | Difference in seroprotection rate |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.5 |
| upper limit | 6.02 |

Notes:

[4] - The upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix hexa(current formulation) minus Infanrix hexa(new formulation)] for the percentage of seroprotected subjects below 10%.

| | |
|-----------------------------------|--|
| Statistical analysis title | Seroprotection rates difference for anti-Polio 2 |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate that the immunogenicity of the Infanrix hexa vaccine (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing Infanrix hexa vaccine one month after a three-dose primary vaccination course.

| | |
|---|---|
| Comparison groups | Infanrix Hexa NEW Group v Infanrix Hexa REF Group |
| Number of subjects included in analysis | 145 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[5] |
| Parameter estimate | Difference in seroprotection rate |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.93 |
| upper limit | 5.66 |

Notes:

[5] - The upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix hexa(current formulation) minus Infanrix hexa(new formulation)] for the percentage of seroprotected subjects below 10%.

| | |
|-----------------------------------|--|
| Statistical analysis title | Seroprotection rates difference for anti-Polio 3 |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate that the immunogenicity of the Infanrix hexa vaccine (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing Infanrix hexa vaccine one month after a three-dose primary vaccination course.

| | |
|---|---|
| Comparison groups | Infanrix Hexa NEW Group v Infanrix Hexa REF Group |
| Number of subjects included in analysis | 145 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[6] |
| Parameter estimate | Difference in seroprotection rate |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.07 |
| upper limit | 5.13 |

Notes:

[6] - The upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix hexa(current formulation) minus Infanrix hexa(new formulation)] for the percentage of seroprotected subjects below 10%.

Primary: Anti-PT, Anti-FHA, Anti-PRN antibody concentrations

| | |
|-----------------|---|
| End point title | Anti-PT, Anti-FHA, Anti-PRN antibody concentrations |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At one month after (POST) Dose 3

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|---|----------------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 128 | 129 | 66 | |
| Units: EL. U/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-PT, POST (N=126,128,66) | 71.8 (64.1 to 80.5) | 74.7 (67.1 to 83) | 75.3 (65.6 to 86.5) | |
| Anti-FHA, POST (N=127,129,66) | 179.7 (158.4 to 203.8) | 215.3 (192.5 to 240.8) | 181.1 (155.8 to 210.6) | |
| Anti-PRN, POST (N=128,129,65) | 143 (122.2 to 167.3) | 142.5 (122.7 to 165.6) | 161.4 (130.6 to 199.6) | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | GMC Ratios for anti-PT |
|----------------------------|------------------------|

Statistical analysis description:

To demonstrate that the immunogenicity of the Infanrix hexa vaccine (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing Infanrix hexa vaccine one month after a three-dose primary vaccination course.

| | |
|---|---|
| Comparison groups | Infanrix Hexa NEW Group v Infanrix Hexa REF Group |
| Number of subjects included in analysis | 257 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[7] |
| Method | ANCOVA |
| Parameter estimate | GMC ratio |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.24 |

Notes:

[7] - The upper limit of the 95% CI on the geometric mean concentrations ratio [DTPa-HBVIPV/ Hib (current formulation) divided by Infanrix hexa(new formulation)] below 1.5.

| Statistical analysis title | GMC Ratios for anti-FHA |
|--|---|
| Statistical analysis description: | |
| To demonstrate that the immunogenicity of the Infanrix hexa vaccine (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing Infanrix hexa vaccine one month after a three-dose primary vaccination course. | |
| Comparison groups | Infanrix Hexa NEW Group v Infanrix Hexa REF Group |
| Number of subjects included in analysis | 257 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[8] |
| Method | ANCOVA |
| Parameter estimate | GMC ratio |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 1.44 |

Notes:

[8] - The upper limit of the 95% CI on the geometric mean concentrations ratio [DTPa-HBVIPV/ Hib (current formulation) divided by Infanrix hexa(new formulation)] below 1.5.

| Statistical analysis title | GMC Ratios for anti-PRN |
|--|---|
| Statistical analysis description: | |
| To demonstrate that the immunogenicity of the Infanrix hexa vaccine (preservative-free formulation) in terms of response to all vaccine antigens is non-inferior to that of the preservative-containing Infanrix hexa vaccine one month after a three-dose primary vaccination course. | |
| Comparison groups | Infanrix Hexa NEW Group v Infanrix Hexa REF Group |
| Number of subjects included in analysis | 257 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[9] |
| Method | ANCOVA |
| Parameter estimate | GMC ratio |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.31 |

Notes:

[9] -

The upper limit of the 95% CI on the geometric mean concentrations ratio [DTPa-HBVIPV/ Hib (current formulation) divided by Infanrix hexa(new formulation)] below 1.5.

Secondary: Number of subjects with vaccine response against PT (anti-PT), FHA (anti-FHA), PRN (anti-PRN) antigens

| | |
|-----------------|--|
| End point title | Number of subjects with vaccine response against PT (anti-PT), FHA (anti-FHA), PRN (anti-PRN) antigens |
|-----------------|--|

End point description:

Vaccine response was defined as the appearance of antibodies in subjects who were initially seronegative (i.e. with concentrations < cut-off value) or at least maintenance of pre-vaccination

antibody concentrations in subjects who were initially seropositive (i.e. with concentrations ³ cut-off value), taking into consideration the decreasing maternal antibodies.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At one month after (POST) Dose 3

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|-------------------------------|----------------------------|----------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 126 | 129 | 65 | |
| Units: Subjects | | | | |
| Anti-PT, POST (N=124,128,65) | 123 | 125 | 65 | |
| Anti-FHA, POST (N=125,129,65) | 123 | 128 | 65 | |
| Anti-PRN, POST (N=126,127,64) | 121 | 124 | 64 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with polyribosyl ribitol phosphate (anti-PRP) antibody concentrations $\geq 1 \mu\text{g/mL}$

| | |
|-----------------|--|
| End point title | Number of subjects with polyribosyl ribitol phosphate (anti-PRP) antibody concentrations $\geq 1 \mu\text{g/mL}$ |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At one month after (POST) Dose 3

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|-------------------------------|----------------------------|----------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 104 | 106 | 54 | |
| Units: Subjects | | | | |
| Anti-PRP, POST (N=104,106,54) | 71 | 82 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti Pertussis toxoid (anti-PT), anti-Filamentous haemagglutinin (anti-FHA) and anti-Pertactin (anti-PRN) antibody concentrations $\geq 5 \text{ EL.U/mL}$

| | |
|----------------------------------|--|
| End point title | Number of subjects with anti Pertussis toxoid (anti-PT), anti-Filamentous haemagglutinin (anti-FHA) and anti-Pertactin (anti-PRN) antibody concentrations ≥ 5 EL.U/mL |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| At one month after (POST) Dose 3 | |

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|-------------------------------|-------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 128 | 129 | 66 | |
| Units: Subjects | | | | |
| Anti-PT, POST (N=126,128,66) | 125 | 128 | 66 | |
| Anti-FHA, POST (N=127,129,66) | 126 | 129 | 66 | |
| Anti-PRN, POST (N=128,129,65) | 127 | 129 | 65 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HBs antibody concentrations

| | |
|----------------------------------|----------------------------------|
| End point title | Anti-HBs antibody concentrations |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| At one month after (POST) Dose 3 | |

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|--|-------------------------|-------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 116 | 123 | 63 | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HBs, POST (N=116,123,63) | 327.6 (268.6 to 399.5) | 313.5 (262.4 to 374.6) | 358.6 (259.8 to 495.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-PRP antibody concentrations

End point title Anti-PRP antibody concentrations

End point description:

End point type Secondary

End point timeframe:

At one month after (POST) Dose 3

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|---|----------------------------|----------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 104 | 106 | 54 | |
| Units: µg/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-PRP, POST (N=104,106,54) | 2.153 (1.59 to 2.915) | 3.034 (2.284 to 4.03) | 0.1 (0.085 to 0.117) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-D, Anti-T antibody concentrations

End point title Anti-D, Anti-T antibody concentrations

End point description:

End point type Secondary

End point timeframe:

At one month after (POST) Dose 3

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|---|----------------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 104 | 106 | 54 | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-D, POST (N=104,106,54) | 0.881 (0.732 to 1.06) | 0.951 (0.777 to 1.164) | 0.875 (0.64 to 1.197) | |
| Anti-T, POST (N=104,106,54) | 2.106 (1.807 to 2.454) | 2.229 (1.958 to 2.539) | 2.225 (1.869 to 2.648) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Polio1, Anti-Polio2, Anti-Polio3 antibody concentrations

| | |
|-----------------|---|
| End point title | Anti-Polio1, Anti-Polio2, Anti-Polio3 antibody concentrations |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At one month after (POST) Dose 3

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|---|----------------------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 71 | 74 | 37 | |
| Units: Titer | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-Polio1, POST (N=60,66,31) | 500.3 (383.8 to 652.3) | 574.9 (423.9 to 779.7) | 566.2 (384.4 to 834) | |
| Anti-Polio2, POST (N=64,74,36) | 399.2 (297.3 to 536) | 390.4 (284.9 to 534.9) | 391.1 (269.6 to 567.3) | |
| Anti-Polio3, POST (N=71,72,37) | 749.3 (592.9 to 946.9) | 686.5 (525.4 to 897.1) | 737.7 (552.3 to 985.4) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms

| | |
|-----------------|--|
| End point title | Number of subjects with solicited local symptoms |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During day 4 (Days 0-3) after each vaccination

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|-------------------------------------|----------------------------|----------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 167 | 167 | 83 | |
| Units: Subjects | | | | |
| Any Pain, D1 (N=167,167,83) | 15 | 18 | 5 | |
| Any Redness, D1 (N=167,167,83) | 40 | 43 | 16 | |
| Any Swelling, D1 (N=167,167,83) | 18 | 19 | 6 | |
| Any Pain, D2 (N=166,167,83) | 15 | 19 | 6 | |
| Any Redness, D2 (N=166,167,83) | 50 | 43 | 22 | |
| Any Swelling, D2 (N=166,167,83) | 21 | 20 | 10 | |
| Any Pain, D3 (N=164,167,82) | 10 | 5 | 3 | |
| Any Redness, D3 (N=164,167,82) | 44 | 48 | 24 | |
| Any Swelling, D3 (N=164,167,82) | 20 | 23 | 10 | |
| Any Pain, Across (N=167,167,83) | 30 | 29 | 13 | |
| Any Redness, Across (N=167,167,83) | 79 | 77 | 36 | |
| Any Swelling, Across (N=167,167,83) | 43 | 44 | 19 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited general symptoms

| | |
|--|--|
| End point title | Number of subjects with solicited general symptoms |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| During day 4 (Days 0-3) after each vaccination | |

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|--|----------------------------|----------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 167 | 167 | 83 | |
| Units: Subjects | | | | |
| Any Drowsiness, D1 (N=167,167,83) | 50 | 49 | 12 | |
| Any Fever (Axillary), D1 (N=167,167,83) | 28 | 41 | 4 | |
| Any Irritability, D1 (N=167,167,83) | 41 | 50 | 15 | |
| Any Loss of appetite, D1 (N=167,167,83) | 19 | 22 | 4 | |
| Any Drowsiness, D2 (N=166,167,83) | 47 | 34 | 13 | |
| Any Fever (Axillary), D2 (N=166,167,83) | 35 | 30 | 13 | |
| Any Irritability, D2 (N=166,167,83) | 42 | 38 | 17 | |
| Any Loss of appetite, D2 (N=166,167,83) | 20 | 19 | 8 | |
| Any Drowsiness, D3 (N=164,167,82) | 22 | 22 | 9 | |
| Any Fever (Axillary), D3 (N=164,167,82) | 18 | 17 | 4 | |

| | | | | |
|---|----|----|----|--|
| Any Irritability, D3 (N=164,167,82) | 25 | 30 | 11 | |
| Any Loss of appetite, D3 (N=164,167,82) | 11 | 12 | 4 | |
| Any Drowsiness, Across (N=167,167,83) | 67 | 64 | 21 | |
| Any Fever (Axillary), Across (N=167,167,83) | 62 | 61 | 18 | |
| Any Irritability, Across (N=167,167,83) | 68 | 74 | 27 | |
| Any Loss of appetite, Across (N=167,167,83) | 39 | 41 | 12 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with unsolicited adverse events

| | |
|-----------------|--|
| End point title | Number of subjects with unsolicited adverse events |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the 31 day (Days 0-30) after each vaccination

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|-----------------------------|----------------------------|----------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 167 | 167 | 83 | |
| Units: Subjects | | | | |
| Any AEs (N=167,167,83) | 40 | 33 | 12 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with serious adverse events

| | |
|-----------------|--|
| End point title | Number of subjects with serious adverse events |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the entire study period

| End point values | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group | |
|-----------------------------|----------------------------|----------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 167 | 167 | 83 | |
| Units: Subjects | | | | |
| Any SAEs (N=167,167,83) | 1 | 3 | 1 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms during the 4-day post-vaccination period, Unsolicited AEs during the 31-day post-vaccination period, SAEs during the entire period.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Infanrix Hexa NEW Group |
|-----------------------|-------------------------|

Reporting group description: -

| | |
|-----------------------|-------------------------|
| Reporting group title | Infanrix Hexa REF Group |
|-----------------------|-------------------------|

Reporting group description: -

| | |
|-----------------------|----------------------|
| Reporting group title | Infanrix Penta Group |
|-----------------------|----------------------|

Reporting group description: -

| Serious adverse events | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group |
|---|-------------------------|-------------------------|----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 3 / 167 (1.80%) | 1 / 83 (1.20%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 167 (0.60%) | 0 / 83 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory disorder | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 167 (0.00%) | 0 / 83 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 167 (0.60%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| Bronchitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 167 (0.60%) | 0 / 83 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 167 (0.00%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Infanrix Hexa NEW Group | Infanrix Hexa REF Group | Infanrix Penta Group |
|---|-------------------------|-------------------------|----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 79 / 167 (47.31%) | 77 / 167 (46.11%) | 36 / 83 (43.37%) |
| General disorders and administration site conditions | | | |
| Pain | | | |
| subjects affected / exposed | 30 / 167 (17.96%) | 29 / 167 (17.37%) | 13 / 83 (15.66%) |
| occurrences (all) | 30 | 29 | 13 |
| Redness | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 79 / 167 (47.31%) | 77 / 167 (46.11%) | 36 / 83 (43.37%) |
| occurrences (all) | 79 | 77 | 36 |
| Swelling | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 43 / 167 (25.75%) | 44 / 167 (26.35%) | 19 / 83 (22.89%) |
| occurrences (all) | 43 | 44 | 19 |
| Drowsiness | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 67 / 167 (40.12%) | 64 / 167 (38.32%) | 21 / 83 (25.30%) |
| occurrences (all) | 67 | 64 | 21 |
| Fever(Axillary) | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 62 / 167 (37.13%) | 61 / 167 (36.53%) | 18 / 83 (21.69%) |
| occurrences (all) | 62 | 61 | 18 |

| | | | |
|--|-------------------------|-------------------------|------------------------|
| Irritability alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 68 / 167 (40.72%) 68 | 74 / 167 (44.31%) 74 | 27 / 83 (32.53%) 27 |
| Loss of appetite alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 39 / 167 (23.35%) 39 | 41 / 167 (24.55%) 41 | 12 / 83 (14.46%) 12 |
| Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) | 13 / 167 (7.78%) 13 | 11 / 167 (6.59%) 11 | 8 / 83 (9.64%) 8 |
| Rhinitis subjects affected / exposed occurrences (all) | 13 / 167 (7.78%) 13 | 5 / 167 (2.99%) 5 | 3 / 83 (3.61%) 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported